FIG. 1-1

human neutral Sphingomyelinase (NSM) Gene Sequence

```
      ACCGCGGCCGTCGCTGGAGAGTTCGAGCCGCCTAGCGCCCCTGGAGCTCCCCAACCATGA
  1 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼T
      TGGCGCCGGCAGCGACCTCTCAAGCTCGGCGGATCGCGGGGACCTCGAGGGGTTGGTACT
                                                                    E I

      AGCCCAACTTCTCCCTGCGACTGCGGATCTTCAACCTCAACTGCTGGTGAGTGCGTCTGC
 61 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼120
      TCGGGTTGAAGAGGGACGCTGACGCCTAGAAGTTGGAGTTGACGACCACTCACGCAGACG

      GGAGTGCGGTCTGGGGGCCACCTTCCGTTCGCACCCATGCAGCCTTCCTCCCCCTATCCC
121 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼180
      CCTCACGCCAGACCCCCGGTGGAAGGCAAGCGTGGGTACGTCGGAAGGAGGGGGATAGGG

      GCCCCACGATCTCAGGGTGTAGGGAAAACCCGAACCTCCAAAGTCCACATCTGGCCCCAG
181 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼240
      CGGGGTGCTAGAGTCCCACATCCCTTTTGGGCTTGGAGGTTTCAGGTGTAGACCGGGGTC

      CGCCGGTGGTCCCAGCAGTCGCCTCCCCTGCCCCGCTCTTCCCTTCCTTAGGGGCATTCC
241 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼300
      GCGGCCACCAGGGTCGTCAGCGGAGGGGACGGGGCGAGAAGGGAAGGAATCCCCGTAAGG

      GTACTTGAGCAAGCACCGGGCCGACCGCATGAGGCGCCTGGGAGACTTTCTGAACCAGGA
301 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼360
      CATGAACTCGTTCGTGGCCCGGCTGGCGTACTCCGCGGACCCTCTGAAAGACTTGGTCCT
                                                                    E II

      GAGCTTCGACCTGGCTTTGCTGGAGGAGGTGAGATTGTGCAGCACGGTGCGGAACCCAGG
361 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼420
      CTCGAAGCTGGACCGAAACGACCTCCTCCACTCTAACACGTCGTGCCACGCCTTGGGTCC

      CTGGGAGGAGGGACAGACCGTCCCACTGGGGAAAGACCAAGCAGGCATCCTCACCGCTTC
421 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼480
      GACCCTCCTCCCTGTCTGGCAGGGTGACCCCTTTCTGGTTCGTCCGTAGGAGTGGCGAAG

      CCTCAGGTGTGGAGTGAGCAGGACTTCCAGTACCTGAGACAGAAGCTGTCACCTACCTAC
481 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼540
      GGAGTCCACACCTCACTCGTCCTGAAGGTCATGGACTCTGTCTTCGACAGTGGATGGATG
                                                                    E III

      CCAGCTGCACACCACTTCCGGAGGTGAGAAGCCCACTGGCCTGAAGCCTGTTGTCATCCC
541 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼600
      GGTCGACGTGTGGTGAAGGCCTCCACTCTTCGGGTGACCGGACTTCGGACAACAGTAGGG

      AGGAGGCTCTTGGCCCTGCCAGCCCTTCCCTATCCTGCCTGCACTCTCCAGTCTCCTCCA
601 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼660
      TCCTCCGAGAACCGGGACGGTCGGGAAGGGATAGGACGGACGTGAGAGGTCAGAGGAGGT

      GCCTCCTCTCCCTCTGGATGTGAGAGAAGGAGAAGGGTGAACCAAGAAGGTCCTATGACT
661 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼720
      CGGAGGAGAGGGAGACCTACACTCTCTTCCTCTTCCCACTTGGTTCTTCCAGGATACTGA

      TCAGCCCCTTTCAGCTTTGTTTTCTGGCTGCCCTATACTCCTCCAAAGGCCGTCGCCTTG
721 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼780
      AGTCGGGGAAAGTCGAAACAAAAGACCGACGGGATATGAGGAGGTTTCCGGCAGCGGAAC

      GTTCTAGGGCTAGTCCCAGCAGTAGAAAAGAAAAAAATAGCTGATCAGAGCTGGAAGAC
781 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼840
      CAAGATCCCGATCAGGGTCGTCATCTTTTTCTTTTTTTATCGAGTAGTCTCGACCTTCTG

      AAGGGAGGGGAAGAAGGCTGGGTGTCTCTCCCTGTTTTTCTGGTTATTAAGCAGGGCTTG
841 ──┼─────────┼─────────┼─────────┼─────────┼─────────┼─────────┼900
      TTCCCTCCCCTTCTTCCGACCCACAGAGAGGGACAAAAAGACCAATAATTCGTCCCGAAC
```

FIG. 1-2

```
    CTCTCCCTCCTTCTCCCCCACATCCTAGCATGAGCCAATGATTCCCTTAGGGCTCTGAGG
1861------------+---------+---------+---------+---------+---------+1920
    GAGAGGGAGGAAGTGGGGGTGTAGGATCGTACTCGGTTACTAAGGGAATCCCGAGACTCC
                                                              E VIII

    AAGGCAACACAATGGTACCCAAGAACTGNTACGTCAGCCAGCAGGAGCTGAAGCCACCCT
1921------------+---------+---------+---------+---------+---------+1980
    TTCCGTTGTGTTACCATGGGTTCTTGACNATGCAGTCGGTCGTCCTCGACTTCGGTGGGA

    CCTTTGGTGTCCGCATTGACTACGTGCTTTACAAGGTCAGGCTCCTCCCTTCAACATGCT
1981------------+---------+---------+---------+---------+---------+2040
    GGAAACCACAGGCGTAACTGATGCACGAAATGTTCCAGTCCGAGGAGGGAAGTTGTACGA

    TTCATATGCTGTGTCTCTTTGTCTAACCTGTGTAGATCCTCCTTTGCTCAGNTAGTCTAG
2041------------+---------+---------+---------+---------+---------+2100
    AAGTATACGACACAGAGAAACAGATTGGACACATCTAGGAGGAAACGAGTCNATCAGATC

    TCTTGGACCACTGATGGGTGGAAAGTGGGGTAGCCGGGAGCTGGTTCTCTGGGAAGAGGC
2101------------+---------+---------+---------+---------+---------+2160
    AGAACCTGGTGACTACCCACCTTTCACCCCATCGGCCCTCGACCAAGAGACCCTTCTCCG

    CCTCATATATAAGCTTCTCTNTGGCCCTTACTTTTCCTAGGCAGTTTCTGGGTTTTACAT
2161------------+---------+---------+---------+---------+---------+2220
    GGAGTATATATTCGAAGAGANACCGGGAATGAAAAGGATCCGTCAAAGACCCAAAATGTA

    CTCCTGTAAGAGTTTTGAAACCACTACAGGCTTTGACCCTNACAGGGGCACCCCCCTCTC
2221------------+---------+---------+---------+---------+---------+2280
    GAGGACATTCTCAAAACTTTGGTGATGTCCGAAACTGGGANTGTCCCCGTGGGGGGAGAG

    TTGATCATGAAGCCCTGATGGCTACTCTGTTTGTGAGGCACAGCCCCCCACAGCAGAACC
2281------------+---------+---------+---------+---------+---------+2340
    AACTAGTACTTCGGGACTACCGATGAGACAAACACTCCGTGTCGGGGGGTGTCGTCTTGG

    CCAGCTCTACCCACGGTGAGTCACCCCCACCCTTTCCTTGGCCCTTGCCCCGCTTGAAGC
2341------------+---------+---------+---------+---------+---------+2400
    GGTCGAGATGGGTGCCACTCAGTGGGGGTGGGAAAGGAACCGGGAACGGGGCGAACTTCG

    AGCCCTTCCACTCTTGACTCTCTCCTGCCCCACTGCCCTGCTCTGTTGTAGGACCAGCAG
2401------------+---------+---------+---------+---------+---------+2460
    TCGGGAAGGTGAGAACTGAGAGAGGACGGGGTGACGGGACGAGACAACATCCTGGTCGTC

    AGAGGTCGCCGTTGATGTGTGTGCTAAAGGAGGCCTGGACGGAGCTGGGTCTGGGCATGG
2461------------+---------+---------+---------+---------+---------+2520
    TCTCCAGCGGCAACTACACACACGATTTCCTCCGGACCTGCCTCGACCCAGACCCGTACC

    CTCAGGCTCGCTGGTGGGCCACCTTCGCTAGCTATGTGATTGGCCTGGGGCTGCTTCTCC
2521------------+---------+---------+---------+---------+---------+2580
    GAGTCCGAGCGACCACCCGGTGGAAGCGATCGATACACTAACCGGACCCCGACGAAGAGG
                                                              E IX

    TGGCACTGCTGTGTGTCCTGGCGGCTGGAGGAGGGGCCGGGGAAGCTGCCATACTGCTCT
2581------------+---------+---------+---------+---------+---------+2640
    ACCGTGACGACACACAGGACCGCCGACCTCCTCCCCGGCCCCTTCGACGGTATGACGAGA

    GGACCCCCAGTGTAGGGCTGGTGCTGTGGGCAGGTGCATTCTACCTCTTCCACGTACAGG
2641------------+---------+---------+---------+---------+---------+2700
    CCTGGGGGTCACATCCCGACCACGACACCCGTCCACGAAAGATGGAGAAGGTGCATGTCC

    AGGTCAATGGCTTATATAGGGCCCAGGCTGAGCTCCAGCATGTGCTAGGAAGGGCAAGGG
2701------------+---------+---------+---------+---------+---------+2760
    TCCAGTTACCGAATATATCCCGGGTCCGACTCGAGGTCGTACACGATCCTTCCCGTTCCC

    AGGCCCAGGATCTGGGCCCAGAGCCTCAGCCAGCCCTACTCCTGGGGCAGCAGGAGGGGG
2761------------+---------+---------+---------+---------+---------+2820
    TCCGGGTGGTAGACCCGGGTCTCGGAGTCGGTCGGGATGAGGACCCCGTCGTCCTCCCCC

    ACAGAACTAAAGAACAATAAAGCTTGGCCCAA
```

FIG. 1-3

2821 TGTCTTGATTTCTTGTTATTTCGAACCGGGTT 2852

FIG. 2-1

Mouse Neutral Sphingomyelinase (nSMase) gene sequence

```
  TNGANNCTGTTAGCTCCAGNCCGGTNGGTCGCCGTNCTAGNCNNATCTNTATAGCTCTTC
1 ------+---------+---------+---------+---------+---------+ 60
  ANCTNNGACAATCGAGGTCNGGCCANCCAGCGGCANGATCNGNNTAGANATATCGAGAAG

   GTTGCGAGCNCAATTNNNTCTCAATAAANGGATNCANCCCTATGACAGAACGTGGACCCC
61 ------+---------+---------+---------+---------+---------+ 120
   CAACGCTCGNGTTAANNNAGAGTTATTTNCCTANGTNGGGATACTGTCTTGCACCTGGGG

    CGCCCGCCANCNCANGNGANACCGCGGCATGGGNCTGAGGTGCNCANGGTGTCTGGGGCG
121 ------+---------+---------+---------+---------+---------+ 180
    GCGGGCGGTNGNGTNCNCTNTGGCGCCGTACCCNGACTCCACGNGTNCCACAGACCCCGC

    AGGGGTTACCTCAGCGATGGTCTTTGACACCTGAAAGCTGGAGCTTTTGAANAGCCCCAN
181 ------+---------+---------+---------+---------+---------+ 240
    TCCCCAATGGAGTCGCTACCAGAAACTGTGGACTTTCGACCTCGAAAACTTNTCGGGGTN

    CACCTTCAGCTTCAGGGGCGGCTCNGGCGGCAACCGCACGTGANATGCTGGGGGCTTCGA
241 ------+---------+---------+---------+---------+---------+ 300
    GTGGAAGTCGAAGTCCCCGCCGAGNCCGCCGTTGGCGTGCACTNTACGACCCCCGAAGCT

    CTTGGGCCGGCACGGNTGCTGGGTGGCCATGGAANNNNACAGNACAGAGCCGGNACACAA
301 ------+---------+---------+---------+---------+---------+ 360
    GAACCCGGCCGTGCCNACGACCCACCGGTACCTTNNNNTGTCNTGTCTCGGCCNTGTGTT

    ATANTGCGAGTCGCCANGGNAACCGCGTGGCTCCTCCCCGAACGCCCNCAAGGGGCGGGA
361 ------+---------+---------+---------+---------+---------+ 420
    TATNTCGCTCAGCGGTNCCNTTGGCGCACCGAGGAGGGGCTTGCGGGNGTTCCCCGCCCT

    CCTGAGTGAGTTCNTGGGCGGGGCCTCNCATCAACTTCAAGCCTGTTGCTGGTGGAAGCC
421 ------+---------+---------+---------+---------+---------+ 480
    GGACTCACTCAAGNACCCGCCCCGGAGNGTAGTTGAAGTTCGGACAACGACCACCTTCGG
E I
    GAGCCGGGAACAAGGGAGGAACCTGTAGGCCGCGGTGCGGATAACCCACCGAAGGACCTA
481 ------+---------+---------+---------+---------+---------+ 540
    CTCGGCCCTTGTTCCCTCCTTGGACATCCGGCGCCACGCCTATTGGGTGGCTTGGTGGAT

    AGAATCTGGAACAGTCCACCCGAGATTCCTTCCAGGACTGCCGGCGGACTCTCGCATTCA
541 ------+---------+---------+---------+---------+---------+ 600
    TCTTAGACCTTGTCAGGTGGGCTCTAAGGAAGGTCCTGAGGGCCGCCTGAGAGCGTAAGT

    GCCCGGGATTTGCAGCCGACCTTCTTTCCGGGTGGAATGACGGCCTTTGTCCCAGTAACG
601 ------+---------+---------+---------+---------+---------+ 660
    CGGGCCCTAAACGTCGGCTGGAAGAAAGGCCCACCTTACTGCCGGAAACAGGGTCATTGC

    CAGGAGTCNNCCCCACCCCCAACCAGCTCGCGTTCCTGGGTCGGGGCAGCGCAGGATAGG
661 ------+---------+---------+---------+---------+---------+ 720
    GTCCTCAGNNGGGGTGGGGGTTGGTCGAGCGCAAGGACCCAGCCCCGTCGCGTCCTATCC
                                                          Start
    GCATAAGCCTGTGCGCGCAAATCCGCCTCGCCGCCCTTGCTCCGAAGCACTCCAGCCATG
721 ------+---------+---------+---------+---------+---------+ 780
    CGTATTCGGACACGCGCGTTTAGGCGGAGCGGCGGGAACGAGGCTTCGTGAGGTCGGTAC

    AAGCTCAACTTTTCTCTACGGCTGAGAGTTTTCAATCTCAACTGCTGgtaagtaagtgct
781 ------+---------+---------+---------+---------+---------+ 840
    TTCGAGTTGAAAAGAGATGCCGACTCTCAAAAGTTAGAGTTGACGACcattcattcacga
```

FIG. 2-2

```
     cccaggcgtgggCTGCAGCCTCGGAGCCACCTTCCAGTCCCCTCTCGCACATGCCTAGGA
841  ------------+---------+---------+---------+---------+---------+ 900
     gggtccgcacccGACGTCGGAGCCTCGGTGGAAGGTCAGGGGAGAGCGTGTACGGATCCT

     AGGAAGCAGGTCTTCTTCAGCCGAGCTAGACCCTGTCCTTCCCGAACCACCAAAGTCCAC
901  ---------+---------+---------+---------+---------+---------+ 960
     TCCTTCGTCCAGAAGAAGTCGGCTCGATCTGGGACAGGAAGGGCTTGGTGGTTTCAGGTG

     ATCGCCTAAAGACCAGAGCTTGGGTGGTTGCAGCAATCACCAAAGTCCCTATCATCCAAA
961  ---------+---------+---------+---------+---------+---------+ 1020
     TAGCGGATTTCTGGTCTCGAACCCACCAACGTCGTTAGTGGTTTCAGGGATAGTAGGTTT

     GCTGAGGTGATGACAGCAGTAATCGTCCCAAACCTGGCCCATGTCTTTCCTTTTAAATGA
1021 ---------+---------+---------+---------+---------+---------+ 1080
     CGACTCCACTACTGTCGTCATTAGCAGGGTTTGGACCCGGTACAGAAAGGAAAATTTACT

     TTTACTTTTATTTTATGTACATTTGGTGTTTTGCCTGTATGTATGTCTGTGTGAAGGTGC
1081 ---------+---------+---------+---------+---------+---------+ 1140
     AAATGAAAATAAAATACATGTAAACCACAAAACGGACATACATACAGACACACTTCCACG

     CAGATTCTCTGGAACTGGAGTTACAGACAGTTGTAAGCTGTCATGTGCTTGCTGGAAATT
1141 ---------+---------+---------+---------+---------+---------+ 1200
     GTCTAAGAGACCTTGACCTCAATGTCTGTCAACATTCGACAGTACACGAACGACCTTTAA

     GAACTGCTGACCCATCTCTTCTGCCCCCTGCGTCCTCCACCCCTTTTAGGGACATCCCCT
1201 ---------+---------+---------+---------+---------+---------+ 1260
     CTTGACGACTGGGTAGAGAAGACGGGGGACGCAGGAGGTGGGGAAAATCCCTGTAGGGGA

     ACCTGAGCAAACATAGGGCGGACCGCATGAAGCGCTTGGGAGACTTTCTGAACTTGGAAA
1261 ---------+---------+---------+---------+---------+---------+ 1320
     TGGACTCGTTTGTATCCCGCCTGGCGTACTTCGCGAACCCTCTGAAAGACTTGAACCTTT
E II

     ACTTTGATCTGGCTCTCCTGGAGGAGGTGAGGTTGTAGGGCAGGCTAGGTTGGAGGAGGG
1321 ---------+---------+---------+---------+---------+---------+ 1380
     TGAAACTAGACCGAGAGGACCTCCTCCACTCCAACATCCCGTCCGATCCAACCTCCTCCC

     CAGCAGGCGGCAGGCGGCGGCAGGAAAACTTGTTCTGTCTTGGGATGAAATCCCAAGCAA
1381 ---------+---------+---------+---------+---------+---------+ 1440
     GTCGTCCGCCGTCCGCCGCCGTCCTTTTGAACAAGACAGAACCCTCCTTTAGGGTTCGTT

     GTATCCTCACCTTCTTCCTCCAGGTGTGGAGTGAGCAGGACTTCCCAGTACCTAAGGCAA
1441 ---------+---------+---------+---------+---------+---------+ 1500
     CATAGGAGTGGAAGAAGGAGGTCCACACCTCACTCGTCCTGAAGGGTCATGGATTCCGTT
E III

     AGGCTATCGCTCACCTATCCAGATGCACACTACTTCAGAAGGTGAAAAGCCTGTGTTCTC
1501 ---------+---------+---------+---------+---------+---------+ 1560
     TCCGATAGCGAGTGGATAGGTCTACGTGTGATGAAGTCTTCCACTTTTCGGACACAAGAG

     AGCCTGTTCTCAGACGAGGAAGCTCTCCAACATTCTTGCTTGCACCCTCGATCTTCTTCC
1561 ---------+---------+---------+---------+---------+---------+ 1620
     TCGGACAAGAGTCTGCTCCTTCGAGAGGTTGTAAGAACGAACGTGGGAGCTAGAAGAAGG

     TCTGGGTCTGAGAAGAGCAGGCCGTCACCCTCATCTTGCAAGGGCTGCTGTCTTAGGCTT
1621 ---------+---------+---------+---------+---------+---------+ 1680
     AGACCCAGACTCTTCTCGTCCGGCAGTGGGAGTAGAACGTTCCCGACGACAGAATCCGAA

     TGTTCTGGGGTTGATCTTAGCAGTAGAGCTGGGAGACCGCGGAGGGGAAGAGGGCTGGCT
1681 ---------+---------+---------+---------+---------+---------+ 1740
     ACAAGACCCCAACTAGAATCGTCATCTCGACCCTCTGGCGCCTCCCCTTCTCCCGACCGA
```

FIG. 2-3

```
     GGGTACTCCCCTCCTTGCTCTTCTGGTTATTAAGCAAGAGTTGGTTTTCAGCGGGATGAT
1741 ------------+---------+---------+---------+---------+---------+ 1800
     CCCATGAGGGGAGGAACGAGAAGACAAATAATTCGTTCTCAACCAAAAGTCGCCCTACTA
E IV

     AGGCAGTGGCCTCTGTGTGTTCTCCAAACACCCAATCCAGGAAATCTTCCAGCATGTCTA
1801 ------------+---------+---------+---------+---------+---------+ 1860
     TCCGTCACCGGAGACACACAAGAGGTTTGTGGGTTAGGTCCTTTAGAAGGTCGTACAGAT

     CAGTCTGAATGGTTACCCCTACATGGTAAGGATCTCTTCCCTATCCTTGCTAACACAGAC
1861 ------------+---------+---------+---------+---------+---------+ 1920
     GTCAGACTTACCAATGGGGATGTACCATTCCTAGAGAAGGGATAGGAACGATTGTGTCTG

     TGGACGCAGCCTTCCTGGGGCCTTGGCAGGAGGGTGTCAGTACCCTGAGTTTTTGTCTTC
1921 ------------+---------+---------+---------+---------+---------+ 1980
     ACCTGCGTCGGAAGGACCCCGGAACCGTCCTCCCACAGTCATGGGACTCAAAAACAGAAG

     TCTTGCCTGCAGTTCCATCATGGAGACTGGTTCTGTGGGAAGTCTGTGGGGCTGCTGGTG
1981 ------------+---------+---------+---------+---------+---------+ 2040
     AGAACGGACGTCAAGGTAGTACCTCTGACCAAGACACCCTTCAGACACCCCGACGACCAC
E V

     CTCCGTCTAAGTGGACTGGTGCTCAATGCTACCGTGACTCATGTGAGTGGGGCTAGCCAG
2041 ------------+---------+---------+---------+---------+---------+ 2100
     GAGGCAGATTCACCTGACCACGTGTTACGATGGCACTGAGTACACTCACCCCGATCGGTC

     GCTTAGGCAGTGGGTCAAGCAGCCCAATGCTATGGTGGAGAAGAGACGCCACTAGTTAGT
2101 ------------+---------+---------+---------+---------+---------+ 2160
     CGAATCGGTCACCCAGTTCCTCGGGTTACGATACCACCTCTTCTCTGCGGTGATCAATCA

     TCTGCTGCCTGGGGATAAGGCATGGGATCAGAAGCTAGCATTGGGCAAGGTTCACCCATT
2161 ------------+---------+---------+---------+---------+---------+ 2220
     AGACGACGGACCCCTATTCCGTACCCTAGTCTTCGATCGTAACCCGTTCCAAGTGGGTAA

     CCCTGTCACACTCTGCCATGTGACAGATGACAAGCTTGATTCAGACAGCCTTCTCTTTGA
2221 ------------+---------+---------+---------+---------+---------+ 2280
     CCCACAGTGTGAGACGGTAGACTGTCTACTGTTCGAACTAAGTCTGTCGGAAGAGAAACT

     TTTCACCTATTCCACTTTAGCTACATGCTGAGTACAGCCGACAGAAGGACATCTACTTTG
1281 ------------+---------+---------+---------+---------+---------+ 2340
     AAAGTGGATAAGGTGAAATCGATGTACGACTCATGTCGGCTGTCTTCCTGTAGATGAAAC
E VI

     CACACCGTGTGGCCCAAGCTTGGGAACTGGCCCAGTTCATCCAGTGTGTGAGCCTGGGCT
2341 ------------+---------+---------+---------+---------+---------+ 2400
     GTGTGGCACACCGGGTTCGAACCCTTGACCGGGTCAAGTAGGTCACACACTCGGACCCGA

     TGATGGGGGCTGTGGGGTGGGGACGGGGTTGAGGGATGNGNAANTTATCCTTGAAGAGGG
2401 ------------+---------+---------+---------+---------+---------+ 2460
     ACTACCCCCGAGTCCCCACCCCTGCCCCAACTCCCTACNCNTTNAATAGGAACTTCTCCC

     CACATAATAAGGGAAGAATTTCCTCCTTGCCGCTCTTCCCCCAACTCAGCCACACATCCA
2461 ------------+---------+---------+---------+---------+---------+ 2520
     GTGTATTATTCCCTTCTTCCCGGAGGAACGGCGAGAAGGGGGTTGAGTCGGTGTGTAGGT
E VII

     AGAATGCAGATGTGGTTCTATTGTGTGGAGACCTCAATATGCACCCCAAAGACCTGGGCT
2521 ------------+---------+---------+---------+---------+---------+ 2580
     TCTTACGTCTACACCAAGATAACACACCTCTGGAGTTATACGTGGGGTTTCTGGACCCGA
```

FIG. 2-4

```
     GCTGCCTGCTGAAAGAGTGGACAGGGCTCCATGATGCTTTCGTTGAGACTGAGGACTTTA
2581 ------------+---------+---------+---------+---------+---------+ 2640
     CGACGGACGACTTTCTCACCTGTCCCGAGGTACTACGAAAGCAACTCTGACTCCTGAAAT

     AGGTGAGAGACTGTTTCCCACCAACTCCACACTTGTTCCAGTCTTCCTGTCTCTTAGCAT
2641 ------------+---------+---------+---------+---------+---------+ 2700
     TCCAGTCTCTCACAAAGGGTGGTTGAGGTGTGAACAAGGTCAGAAGGACAGAGAATCGTA

     CCTAGCCACCTGTTTCCCTAGGGCTCTGATGATGGCTGTACCATGGTACCCAAGAACTGC
2701 ------------+---------+---------+---------+---------+---------+ 2760
     GGATCGGTGGACAAAGGGATCCCGAGACTACTACCGACATGGTACCATGGGTTCTTGACG
E VIII
     TACGTCAGCCAGCAGGACCTGGGACCGTTTCCGTCTGGTATCCGGATTGATTACGTGCTT
2761 ------------+---------+---------+---------+---------+---------+ 2820
     ATGCAGTCGGTCGTCCTGGACCCTGGCAAAGGCAGTCCATAGGCCTAACTAATGCACGAA

     TACAAGGTCAGGCTCTTATTCCCGGTGTGCCTTCTCCAGTATCTTCCTTCCTCTGTCACT
2821 ------------+---------+---------+---------+---------+---------+ 2880
     ATGTTCCAGTCCGAGAATAAGGGCCACACGGAAGAGGTCATAGAAGGAAGGAGACAGTGA

     AGCCCACGCTTTAGTTCAGCTACAGTCTTGGGCCACTGATGGCTAAAGAATAGAATCCTG
2881 ------------+---------+---------+---------+---------+---------+ 2940
     TCGGGTGCGAAAGCAAGTCGATGTCAGAACCCGGTGACTACCGATTTCTTATCTTAGGAC

     TCGGCTGGTTCTCTGGGAGAATTTAAGCTTCTCCATGTTCTTGCTCTTCCTAGGCAGTCT
2941 ------------+---------+---------+---------+---------+---------+ 3000
     AGCCGACCAAGAGACCCTCTTAAATTCGAAGAGGTACAAGAACGAGAAGGATCCGTCAGA

     CTGAGTCCCACGTCTGCTGTGAGACTCTGAAAACCACTACAGGCTGTGACCCTCACAGTG
3001 ------------+---------+---------+---------+---------+---------+ 3060
     GACTCAGGGTGCAGACGACACTCTGAGACTTTTGGTGATGTCCGACACTGGGAGTGTCAC
E IX
     ACAAGCCCTTCTCTGATCACGAGGCCCTCATGGCTACTTTGTATGTGAAGCACAGCCCCC
3061 ------------+---------+---------+---------+---------+---------+ 3120
     TGTTCGGGAAGAGACTAGTGCTCCGGGAGTACCGATGAAACATACACTTCGTGTCGGGGG

     CTCAGGAAGACCCCTGTACTGCCTGTGGTAAGCAGCATTTCCTTTGCCCCCTCTACTTTA
3121 ------------+---------+---------+---------+---------+---------+ 3180
     GAGTCCTTCTGGGGACATGACGGACACCATTCGTCGTAAAGGAAACGGGGGAGATGAAAT

     AGGCAGCCCCGCCTCCATCCTGACCCTCCCCTGCTCTACGTTCTCTCTTTTTCCAGGCCC
3181 ------------+---------+---------+---------+---------+---------+ 3240
     TCCGTCGGGGCGGAGGTAGGACTGGGAGGGGACGAGATGCAAGAGAGAAAAAGGTCCGGG

     ACTGGAAAGGTCCGATTTGATCAGCGTGCTAAGGGAGGCCAGGACAGAGCTGGGGCTAGG
3241 ------------+---------+---------+---------+---------+---------+ 3300
     TGACCTTTCCAGGCTAAACTAGTCGCACGATTCCCTCCGGTCCTGTCTCGACCCCGATCC
E X
     CATAGCTAAAGCTCGCTGGTGGGCTGCATTCTCTGGCTATGTGATCGTTTGGGGGCTGTC
3301 ------------+---------+---------+---------+---------+---------+ 3360
     GTATCGATTTCGAGCGACCTCCCGACGTAAGAGACCGATACACTAGCAAACCCCCGACAG

     CCTTCTGGTGTTGCTGTGTGTCCCGGCTGCAGGAGAAGAGGCCAGGGAAGTGGCCATCAT
3361 ------------+---------+---------+---------+---------+---------+ 3420
     GGAAGACCACAACGACACACAGGGCCGACGTCCTCTTCTCCGGTCCCTTTACCGGTACTA
```

FIG. 2-5

```
     CCTCTGCATACCCAGTGTGGGTCTGGTGCTGGTAGCAGGTGCAGTCTACCTCTTCCACAA
3421 ------------+---------+---------+---------+---------+---------+ 3480
     GGAGACGTATGGGTCACACCCAGACCACGACCATCGTCCACGTCAGATGGAGAAGGTGTT

     GCAGGAGGCCAAGGGCTTATGTCGGGCCCAGGCTGAGATGCTGCACGTTCTGACAAGGGA
3481 ------------+---------+---------+---------+---------+---------+ 3540
     CGTCCTCCGGTTCCCGAATACAGCCCGGGTCCGACTCTACGACGTGCAAGACTGTTCCCT

     AACGGAGACCCAGGACCGAGGCTCAGAGCCTCACCTAGCCTACTGCTTGCAGCAGGAGGG
3541 ------------+---------+---------+---------+---------+---------+ 3600
     TTGCCTCTGGGTCCTGGCTCCGAGTCTCGGAGTGGATCGGATGACGAACGTCGTCCTCCC

                      stop
     GGACAGAGCTTAAGAGCTTAACAATAAAACTTGCTTGACACACTCTAGTGGCTCTACCTT
3601 ------------+---------+---------+---------+---------+---------+ 3660
     CCTGTCTCGAATTCTCGAATTGTTATTTTGAACGAACTGTGTGAGATCACCGAGATGGAA

     GTTCCTTGCAGAGGCATGATGGGAACTGAAGGTCAGTGGCCTTGTCACTGTGTGGCTTTA
3661 ------------+---------+---------+---------+---------+---------+ 3720
     CAAGGAACGTCTCCGTACTACCCTTGACTTCCAGTCACCGGAACAGTGACACTCCGAAAT

     GAGCGTTGGCCTCTCACTTGCCTTTTTTGCACACTCCCGTCTCCTGCCAGCACAGAGCAT
3721 ------------+---------+---------+---------+---------+---------+ 3780
     CTCGCAACCGGAAAGTGAACGGAAAAAACGTGTGAGGGCAGAGGACGGTCGTGTCTCGTA

     AAACCCTGTTCATGGTCATAATCCTTTTATTGTAAACAACGAAGCCTCTGACTAAGCAGT
3781 ------------+---------+---------+---------+---------+---------+ 3840
     TTTGGGACAAGTACCAGTATTAGGAAAATAACATTTGTTGCTTCGGAGACTGATTGGTCA

     CCAGATGGCGGAGGTACAGCCCTTGTGATGGTGTCTTGCTTACGGGGCAGGGAGGCAGCT
3841 ------------+---------+---------+---------+---------+---------+ 3900
     GGTCTACCGCCTCCATGTCGGGAACACTGCGACAGAACGAATGCCCCGTCCTCCGTCGA

     AACCATCATCTTCTAGCCCTGGGCTCCCATCTATGCAGGCATCTCTCTGAGCCTCCGTTC
3901 ------------+---------+---------+---------+---------+---------+ 3960
     TTGGTAGTAGAAGATCGGGACCCGAGGGTAGATACGTCCATCTAGAGACTCGGAGGCAAG

     CTCCTGGAATTGGNTCAGAGCAATCCCGCTTGGTTCACCAACCTCCAAACAGCTTCCTTA
3961 ------------+---------+---------+---------+---------+---------+ 4020
     GAGGACCTTAAGGNAGTCTCGTTAGGGCGAACCAAGTGGGTGGAGGTTTGTCGCCTTCCT

     AGGACCTGGTTTCTCAAAANGGNAAGGTNCGGGCCTCCGGTCTTCAATANGTTTTCCTAA
4021 ------------+---------+---------+---------+---------+---------+ 4080
     TCCTGGGCCAAAGAGTTTTNCCNTTCCANCGGGGGTGGCCAGAAGTTATNCAAAAGGATT

     AAAGGGANGAATGAAAANCCTTAAGNNCCAACAAGGGGAACCCTTGGNCCCAAAAGGGGA
4081 ------------+---------+---------+---------+---------+---------+ 4140
     TTTCCCTNCTTACTTTTNGGAATTCNNGGTTGTTCCCCTTGGGAACCNGGGTTTTCCCCT

     CCTGGGTGGTTTCCCNTTGGGGCCAAANTTATCCCAAAGGGGTCCAATTGAAGGGTTAAC
4141 ------------+---------+---------+---------+---------+---------+ 4200
     GGACCCACCAAAGGGNAACCCCGGTTTNAATAGGGTTTCCCCACCTTAACTTCCCAATTG

     CCCCCAAAAAANNACCCNTTTCCCCCGGAATTTCCAAAGGTTTNCCCCCCCCGGCAAAANC
4201 ------------+---------+---------+---------+---------+---------+ 4260
     GGGGGTTTTTNNTGGGNAAAGGGGGCCTTAAAGGTTTCCAAANGGGGGGGGCCGTTTTNG
```

FIG. 2-6

```
    TCCCTTGGGGNNCCNAANCCNTGGCCCGGNCTTGGCTTTTCCCCCTTTCCCAAGNATTTC
4261---------+---------+---------+---------+---------+---------+4320
    AGGGAACCCCNNGGNTTNGGNACCGGGCCNGAACCGAAAAGGGGGAAAGGGTTCNTAAAG
```

```
    AAANNTTCCCTNGGAAANCCCCTTGNTTGGNAAAACCNAATNANGAACCANGCCAANNNT
4321---------+---------+---------+---------+---------+---------+4380
    TTTNNAAGGGANCCTTTNGGGGAACNAACCNTTTTGGNTTANTNCTTGGTNCGGTTNNNA
```

```
    TGCCAANAAACCNTTTGGGCAAAGGGGGNAAATTCANCAANGGGGNAATTGGGGAAACCC
4381---------+---------+---------+---------+---------+---------+4440
    ACGGTTNTTTGGNAAACCCGTTTCCCCCNTTTAAGTNGTTNCCCCNTTAACCCCTTTGGG
```

```
    NTGGGTTTNCCCAAAGGGCCCNAANANT
4441---------+---------+--------4468
    NACCCAAANGGGTTTCCCGGGNTTNTNA
```

FIG. 3

A

396 bp —

B

298 bp —

C

45 kDa —

HEK mock-transf.
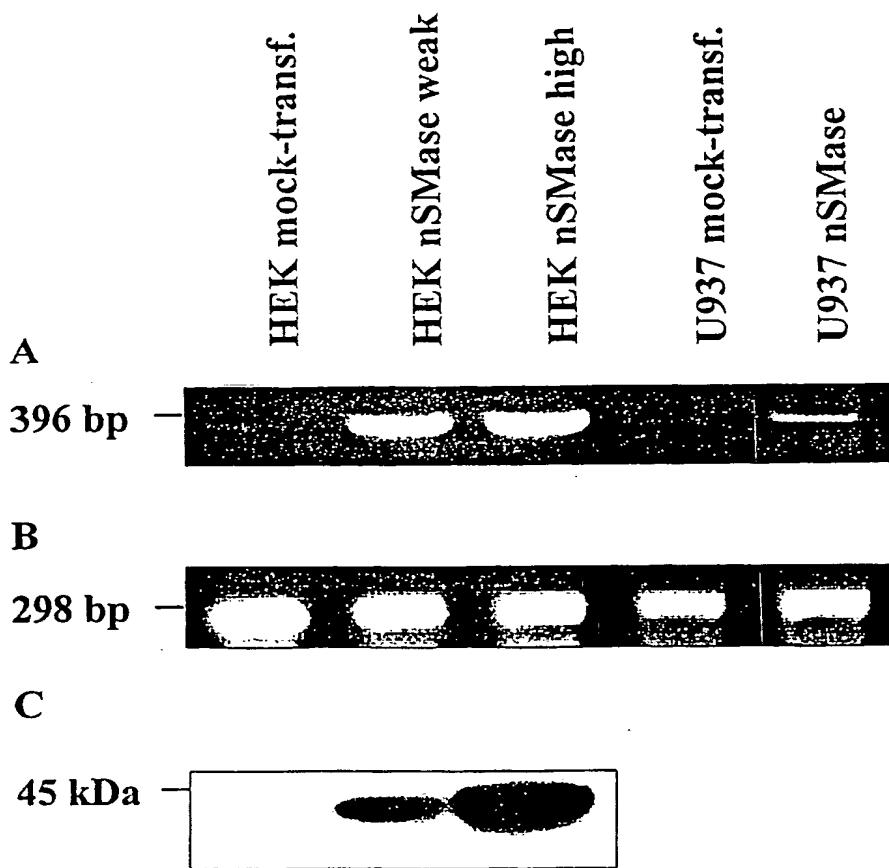
HEK nSMase weak

HEK nSMase high

U937 mock-transf.

U937 nSMase

FIG. 4

mnSMase "konventional" Knock Out
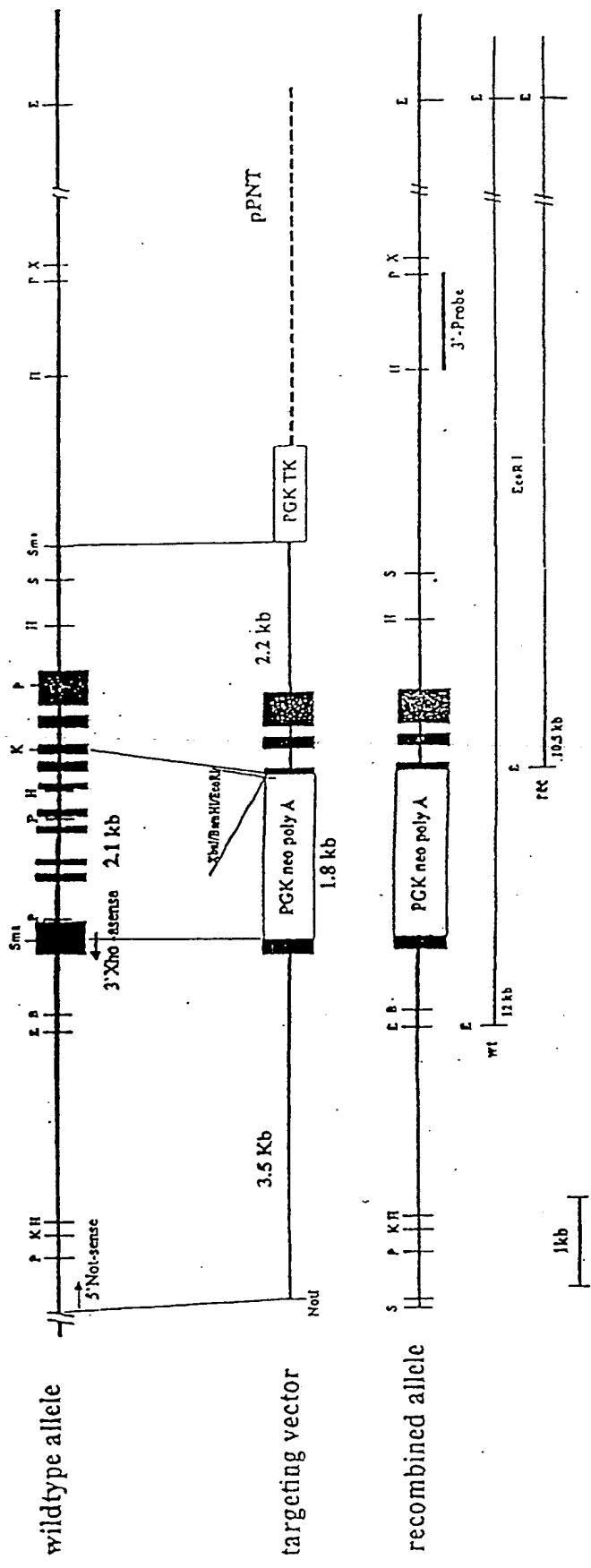
FIG. 5

Constructs for generating transgenic mouse mutants

ubiquitin promoter	nSMase	IRES	lacZ	polyA

polyA	rtTA	CMV	CMV-1	nSMase	IRES	GFP	polyA
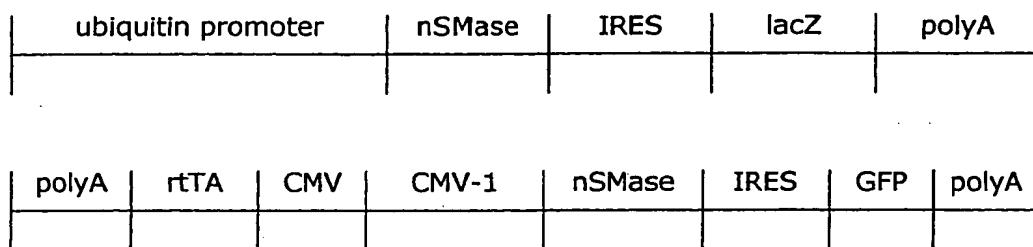
Ubiquitin promoter:	regulatory sequence of the ubiquitin gene, controlling a ubiquitous transcription.
nSMase:	neutral sphingomyelinase
lacZ:	lacZ, gene coding for β-galactosidase
polyA:	recognition signal for the termination of transcription and polyadenylation
CMV:	cytomegalovirus promoter of the cytomegalovirus gene, controlling a ubiquitous transcription.
rtTA:	reverse transactivator, binds to the minimal promoter and thus controls transcription. The binding properties of the transactivator are influenced by tetracyclin. The addition of tetracyclin makes the transactivator bind to the minimal promoter and starts transcription, removal of tetracyclin prevents the binding of the transactivator to the minimal promoter and prevents transcription.
CMV-1:	minimal promoter, binding of transactivator starts transcription.
IRES:	*internal ribosomal entry sequence*, viral initiation signal for translation.